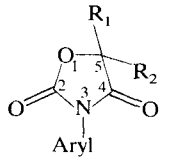
# $^{1}H$ and $^{13}C$ NMR Studies on 3-Aryl-5-alkyl-2,4-oxazolidinediones. The Magnetic Non-equivalence of Isomeric Nuclei†

**Sıddık İçli**
Department of Chemistry, Middle East Technical University, Ankara, Turkey

**Magnetic non-equivalence of diastereotopically related proton and $^{13}C$ nuclei in enantiomeric and diastereomeric rotational isomers of 3-aryl-5-alkyl-2,4-oxazolidinediones has been investigated. Steric interactions between the aryl and the heterocyclic moieties of these compounds produce sufficient restriction to rotation about the aryl C—N bond that the presence of torsional isomers may be detected at normal temperatures. Free energies of activation for rotation have been calculated. Chemical shift differences, associated with rotational isomerism, may be detected for both the proton and the $^{13}C$ nuclei on the hetero ring, but only in the $^{13}C$ spectra of the nuclei on the aryl moiety.**

## INTRODUCTION

In a chiral molecule, pairs of nuclei which reside in diastereotopically related environments should, in principle, display differences in their properties. This is also true of corresponding nuclei in diastereomers. For example, such nuclei are magnetically non-equivalent and may show recognizable differences in their magnetic resonance spectra, provided that certain criteria are satisfied. The circumstances under which magnetic non-equivalence is observable, and the information which can be obtained from such non-equivalence, have been the subject of many investigations.[1] For substantial differences to be observable in the chemical shifts of diastereotopically related nuclei in conformationally mobile molecules with rate dependent spectra, it has usually been considered necessary that the molecules have a preferred conformation(s) in which the members of the pair of nuclei reside in quite different magnetic environments. The occurrence or non-occurrence of observable magnetic non-equivalence may thus provide a rather sensitive probe for studying conformational preferences. A disadvantage of the method is that, in many cases, the chemical shift differences are too small to be observed. However, when molecular dissymmetry is accompanied by steric interactions which force major differences between conformations, and when magnetically anisotropic groupings are present, appreciable chemical shift differences may be observable.[2]



| | $R_1$ | $R_2$ | Aryl |
|---|---|---|---|
| **1:** | $CH_3$ | H | Phenyl |
| **2:** | $CH_3$ | H | *o*-Tolyl |
| **3:** | $CH_3$ | H | 2,5-Dimethylphenyl |
| **4:** | $CH_3$ | H | *o*-Chlorophenyl |
| **5:** | $CH_3$ | H | α-Naphthyl |
| **6:** | $CH_3$ | $CH_3$ | Phenyl |
| **7:** | $CH_3$ | $CH_3$ | *o*-Tolyl |
| **8:** | $CH_3$ | $CH_3$ | α-Naphthyl |

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This study reports the observation of magnetic non-equivalence of diastereotopically related proton and carbon nuclei in 3-aryl-5-alkyl-2,4-oxazolidinediones. These observations are discussed in terms of the stereochemistry of these molecules and the effects of substituents. The measurements were made in the absence of extreme solute–solvent interactions,[3] which may enhance chemical shift differences.

Those 3-aryl-5-alkyl-2,4-oxazolidinedione molecules with *ortho* substituents on the aryl group are expected to have two relatively stable conformations, corresponding to the ground states for internal rotation about the aryl C—N bond. Steric interactions between the aryl and the heterocyclic moieties are likely to result in large dihedral angles between the two groups in the ground states (see Fig. 1). If the substituents on C-5 are identical (**7**, **8**) the rotational isomers of the *ortho* substituted compounds are enantiomeric, and are expected to exhibit identical NMR spectra in achiral solvents. However, the C-5 substituents are diastereotopically related and should, in principle, display magnetic non-equivalence, provided that the rate of internal rotation is slow on the NMR time scale. When the substituents on C-5 are different

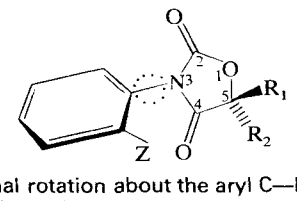

**Figure 1.** Internal rotation about the aryl C—N bond in 3-aryl-5-alkyl-2,4-oxazolidinediones.

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(**2–5**) the rotational isomers of the *ortho* substituted compounds are diastereomers, and should have distinctly different NMR spectra if internal rotation is sufficiently slow. In particular, corresponding pairs of nuclei in the two diastereomeric rotamers should show chemical shift differences. The magnitude of the chemical shift differences must be related to factors such as the rate of internal rotation, steric effects which determine dihedral angles, and anisotropic and electronic effects of substituents.

If the rate of internal rotation is fast on the NMR time scale, the pairs of signals produced by diastereotopic nuclei will collapse to singlets. Thus, evidence for conformational isomerism in compounds of this type is directly observable only below the coalescence points of these signals. The barriers to internal rotation may be conveniently calculated for the measured coalescence temperatures.[4]

## EXPERIMENTAL

The 3-aryl-5-alkyl-2,4-oxazolidinediones were prepared by the reaction of aryl isocyanates with α-hydroxycarboxylic acid esters.[5] Conversions of appropriate benzoyl chlorides to the corresponding aryl isocyanates were carried out in the presence of sodium azide. Substituted benzoyl chlorides were prepared from benzoic acid derivatives by reaction with excess thionyl chloride. The oxazolidinediones were purified by crystallization, and were identified by their IR and $^1$H NMR spectra (see Table 1 for the melting points and the analytical data).

*3-(o-Tolyl)-5-methyl-2,4-oxazolidinedione.* *o*-Toluic acid (13.6 g, 0.1 mole) was stirred overnight in excess thionyl chloride (47.2 g, 0.4 mole). The reaction was completed under reflux on a water bath for 1–2 h and the excess thionyl chloride was distilled from the reaction mixture. The remaining crude *o*-toluoyl chloride was then fractionally distilled and identified [IR (C=O) 1775 cm$^{-1}$; b.p. 200 °C; yield 13.5 g, 87%]. *o*-Toluoyl chloride (13.5 g, 0.086 mole) and sodium azide (7.8 g, 0.120 mole) were refluxed in benzene (20 ml) for 6 h. *o*-Tolyl isocyanate was distilled from the reaction mixture and purified by fractional distillation [IR (N=C=O) 2230 cm$^{-1}$; b.p. 184–7 °C; yield 4.76 g, 42%]. *o*-Tolyl isocyanate (4.44 g, 0.033 mole) and L(+)-ethyl lactate (3.96 g, 0.033 mole) were mixed in toluene (20 ml) before sodium metal (0.76 g, 0.033 mole) was added. The reaction mixture was refluxed for 3 h at 76–8 °C. The ethanol formed during the reaction was distilled off and the reaction mixture was refluxed at 110 °C for 1 h. The resulting crude 3-(*o*-tolyl)-5-methyl-2,4-oxazolidinedione was purified by crystallization from toluene and benzene [IR (C=O) 1825 cm$^{-1}$ and 1745 cm$^{-1}$; m.p. 103–4 °C; yield 3.21 g, 47%].

The IR spectra were taken in chloroform or carbon tetrachloride using a Beckman IR-18A spectrophotometer. Elemental analyses were obtained from a Coleman Model 33 C, H analyzer. The $^1$H NMR spectra were recorded using a Varian T-60A spectrometer. The $^{13}$C NMR measurements were carried out at the Varian NMR applications laboratory in Switzerland or recorded at the University of Ankara using a Varian CFT-20 $^{13}$C NMR spectrometer. The assignments of the carbon chemical shifts were based on the analysis of proton decoupled and coupled spectra, considering mesomeric and structural effects. Both the $^1$H and $^{13}$C NMR samples were prepared in $CDCl_3$ at 0.2–0.5 M concentrations. Pyridine was used as a solvent for the temperature studies and the temperatures at which the $^1$H NMR spectra were recorded were measured using an ethylene glycol sample, with an estimated accuracy of ±1 °C.

**Table 1. Melting points and the analytical data of the synthesized 3-aryl-5-alkyl-2,4-oxazolidinediones**

| Compound | M.p. (°C) | Calculated %C | Calculated %H | Found %C | Found %H |
|---|---|---|---|---|---|
| **1** | 141 | 62.82 | 4.74 | 62.18 | 4.71 |
| **2** | 103–4 | 64.38 | 5.40 | 63.89 | 5.48 |
| **3** | 94 | 65.74 | 5.97 | 65.39 | 5.87 |
| **4** | 83 | 53.19 | 3.58 | 52.82 | 3.69 |
| **5** | 127 | 69.92 | 4.59 | 69.90 | 4.89 |
| **6** | 107 | 64.38 | 5.40 | 65.08 | 5.32 |
| **7** | 92–3 | 65.74 | 5.97 | 65.54 | 5.96 |
| **8** | 138 | 70.59 | 5.10 | 71.20 | 5.41 |

## RESULTS AND DISCUSSION

### $^1$H NMR Spectra

The 3-aryl-5-alkyl-2,4-oxazolidinediones lacking *ortho* aryl substituents (**1**, **6**) may undergo degenerate rotational isomerism about the aryl C—N bond, and they exhibited the $^1$H NMR spectra expected for such compounds. All the *ortho* substituted compounds examined (**2–5**, **7**, **8**) exhibited proton spectra with additional splittings resulting from restricted internal rotation about the torsional axis. Thus, the rates of internal rotation in these compounds are slow on the NMR time scale at normal temperatures. That the additional signals were due to restricted internal rotation was confirmed by observing the reversible collapse of the doubled signals at high temperatures (Table 2).

**Table 2. Magnetic non-equivalence of the methyl and methine protons of some 3-aryl-5-alkyl-2,4-oxazolidinediones[a]**

| | Aryl | Methyl[b] δ | Methyl[b] Δδ | Methine[b] δ | Methine[b] Δδ |
|---|---|---|---|---|---|
| | | C-5 Monomethyl | | | |
| **2** | o-Tolyl | 1.63 | 0.00 | 5.02<br>5.09 | 0.07 |
| **3** | 2,5-Dimethylphenyl | 1.68 | 0.00 | 5.17<br>5.21 | 0.04 |
| **4** | o-Chlorophenyl | 2.70<br>2.72 | 0.02 | 5.20<br>5.27 | 0.07 |
| **5** | α-Naphthyl | 1.56<br>1.62 | 0.06 | 5.10<br>5.12 | 0.11 |
| | | C-5 Dimethyl | | | |
| **8** | α-Naphthyl | 1.58<br>1.66 | 0.08 | — | — |

[a] In ppm from TMS.
[b] Methyl and methine protons on C-5.

When the *ortho* aryl substituent was a methyl group (**2** and **3**) only the C-5 methine proton signals of the diastereomeric rotamers were distinguishable in the $^1$H NMR spectra. Thus, the C-5 proton appears to be a more sensitive probe for molecular dissymmetry than the methyl protons. The spectrum of **4** shows evidence for the polar influence of an *ortho* chloro substituent, since, in this case, the signals of the 5-methyl groups of the diastereomeric rotamers were distinguishable. The greater influence of the chloro than the methyl substituent is attributed, in part, to repulsive interaction between the chlorine atom and the carbonyl oxygen atoms of the hetero ring, with a consequent effect on the dihedral angle between the two rings. Since the observed chemical shift differences between diastereotopically related nuclei on the heterocyclic moiety must result from the magnetic anisotropy of the aryl group and its substituents, these differences should be sensitive to changes in dihedral angle.

The enhanced magnetic anisotropy and the large steric effect of the $\alpha$-naphthyl group in **5** result in the largest chemical shift differences between diastereomeric rotamers in this series, 0.06 and 0.11 ppm for the 5-methyl and the C-5 methine signals, respectively. An $\alpha$-naphthyl group has been previously shown to produce substantial barriers to rotation about an aryl C—N bond.[2]

Similar enhancement of the chemical shift differences resulting from restricted internal rotation is evident on comparison of the spectral data for **7** and **8**. In these cases, the rotational isomers are enantiomers, but the C-5 methyl groups are diastereotopically related within each isomer. Magnetic non-equivalence of the 5-methyl signals was not seen for the 3-(*o*-tolyl) compound, **7**. In view of the high coalescence temperature for the corresponding 5-monomethyl compound, **2**, it is unlikely that the lack of observable splitting in **7** was due to fast rotation about the pivot bond. In **8**, where the aryl moiety is $\alpha$-naphthyl, separate signals were observed for the 5-methyl groups, with a chemical shift difference of 0.08 ppm, due to the unequal anisotropic influence of the aromatic system.

No splitting of the signals arising from methyl groups attached to the aromatic ring was observed for those cases (**2**, **3**) in which separate signals are stereochemically possible.

## $^{13}$C NMR Spectra

**Carbonyl carbons and aliphatic carbons.** Although, in principle, separate signals from corresponding carbonyl carbon atoms of the diastereomeric rotamers are expected, none were observed (Table 3). Thus, the carbonyl carbons are not useful probes for the detection of this type of rotational isomerism, despite their close proximity to the aryl group.

However, the 5-carbon atoms of the diastereomeric rotational isomers of the 2,5-dimethylphenyl, (**3**), and the *o*-chlorophenyl, (**4**), compounds showed distinct signals (Table 3). In this respect, the behaviour of the oxazolidinediones differs from that of previously studied and closely related 1-arylhydantions, which showed no splitting of the 5-carbon signals for the corresponding rotational isomers.[6]

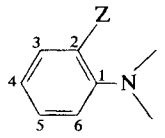
All the rotational isomers, diastereomeric and enantiomeric, displayed separate signals for the carbon atoms of the methyl groups attached to the 5-position of the hetero ring. The greater sensitivity of the carbon spectrum than the proton spectrum to differences in the magnetic environments of the 5-methyl groups suggests that $^{13}$C NMR may be a better technique than $^1$H NMR for studying systems such as these. The diastereotopic splittings were easily observable in the carbon spectra of the enantiomeric rotamers, in contrast to the proton spectra. For example, a chemical shift difference of 0.66 ppm was observed for the 5-dimethyl carbon signals of **7**, whereas no chemical shift difference was observable in the proton spectrum.

**Table 3. Aliphatic and carbonyl carbon shieldings of some 3-aryl-5-alkyl-2,4-oxazolidinediones[a]**

| | Aryl | C-2 | C-4 | C-5 | $CH_3$[b] | $CH_3$[c] | $CH_3$[d] |
|---|---|---|---|---|---|---|---|
| | | | | C-5 Monomethyl | | | |
| **1** | Phenyl | 153.93 | 172.37 | 75.84 | 16.66 | — | — |
| **2** | o-Tolyl | 153.88 | 172.57 | 76.33 | 16.98<br>16.55 | 17.49<br>17.30 | — |
| **3** | 2,5-Dimethylphenyl | 153.98 | 172.64 | 76.36<br>76.29 | 16.92<br>16.80 | 17.16 | 20.72 |
| **4** | o-Chlorophenyl | 152.28 | 170.94 | 69.58<br>61.41 | 17.08<br>14.11 | — | — |
| **5** | α-Naphthyl | 154.17 | 172.96 | 76.50 | 17.33<br>16.81 | — | — |
| | | | | C-5 Dimethyl | | | |
| **6** | Phenyl | 153.38 | 175.26 | 83.75 | 24.03 | — | — |
| **7** | o-Tolyl | 153.16 | 174.99 | 83.83 | 24.26<br>23.60 | 17.33 | — |
| **8** | α-Naphthyl | 153.53 | 175.43 | 84.12 | 24.02<br>23.38 | — | — |

[a] In ppm from TMS.
[b] Methyl carbon on C-5.
[c] *ortho*-Methyl carbon on aryl ring.
[d] The 5-methyl carbon on the phenyl ring.

**Table 4. Aryl carbon shieldings of some 3-aryl-5-alkyl-2,4-oxazolidinediones[a]**



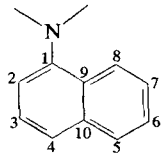
| | Aryl | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| | | | | C-5 Monomethyl | | | |
| 1 | Phenyl | 131.00 | 125.54 | 129.28 | 128.81 | 129.28 | 125.54 |
| 2 | o-Tolyl | 135.95<br>135.82 | 129.62 | 131.29 | 128.05<br>127.98 | 129.96 | 127.06 |
| 3 | 2,5-Dimethylphenyl | 137.12<br>137.20 | 129.18 | 131.17 | 130.96 | 132.59<br>132.16 | 128.40<br>128.27 |
| 4 | o-Chlorophenyl | 134.51 | 122.36 | 127.73 | 124.02 | 129.09 | 120.21 |
| | | | | C-5 Dimethyl | | | |
| 6 | Phenyl | 131.56 | 126.03 | 129.59 | 129.11 | 129.59 | 126.03 |
| 7 | o-Tolyl | 135.83 | 129.73 | 129.93 | 128.06 | 131.29 | 127.09 |

[a] In ppm from TMS.

The carbon atoms of the aryl methyl groups, in contrast to the protons of these groups, showed magnetic non-equivalence (0.2 ppm) in the diastereomeric rotamers of the 3-(*o*-tolyl) compound (**2**). However, similar splitting was not observed for the stereochemically similar 3-(2,5-dimethylphenyl) compound, (**3**).

Observed chemical shift differences between diastereomeric rotamers, and within enantiomeric rotamers, ranged from 0.1 to 0.7 ppm, except in the case of the *ortho* chloro compound, (**4**). This compound exhibited exceptionally large chemical shift differences of 3 ppm and 8 ppm for the 5-methyl and C-5, respectively. Carbon chemical shift differences in this series must arise, in part, from differences in the effects of the magnetic anisotropy of the aryl group and its substituents, but the greater chemical shift differences in the carbon than the proton spectra indicate that factors other than aryl group anisotropy are dominant in determining the separation of carbon signals.

**Table 5. Naphthyl carbon shieldings of some 3-aryl-5-alkyl-2,4-oxazolidinediones[a]**



| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 8 | 134.41 | 121.28 | 130.53 | 125.27 | 127.53 |
| 5 | 134.46 | 121.62<br>121.23 | 130.64 | 125.34<br>125.29 | 127.60<br>127.53 |
| | 6 | 7 | 8 | 9 | 10 |
| 8 | 126.73 | 126.46 | 128.75 | 126.94 | 129.27 |
| 5 | 126.82 | 126.51<br>126.36 | 128.81<br>128.75 | —[b] | 129.30 |

[a] In ppm from TMS.
[b] Overlapped.

**Aromatic carbon atoms.** In the achiral solvent used, rotational isomerism can, in principle, be detected only in the spectra of the aromatic carbon atoms of those compounds with diastereomeric rotamers. Hence the spectra of **1**, and **6–8**, which have degenerate or enantiomeric rotamers, showed the expected single line for each carbon atom (Tables 4 and 5). In contrast, many of the aryl carbon signals of those compounds with diastereomeric rotamers split into two components (Tables 4 and 5). It is difficult to predict which aryl carbons will produce twin signals in these compounds, since the observed differences were small (between 0.05 and 0.45 ppm) and irregular. Splitting of aromatic carbon signals as a result of low rates of conformational isomerism has been reported previously, as in the study of aromatic aldehydes at low temperatures.[7]

**Barriers to internal rotation.** Free energies of activation ($\Delta G^{\neq}$) were calculated for the coalescence points of the temperature dependent spectra in pyridine solutions (Table 6). The numbers are approximate in the cases of those compounds with diastereomeric rotamers, since the intensities of the two lines were not exactly 1 : 1 but the calculation is more accurate for **8**, since the lines were of equal intensity in the spectrum of this compound.

The measured free energies of activation show that steric interactions between the aryl and the heterocyclic moieties of these compounds produce substantial

**Table 6. The coalescence temperatures and the free energies of activation calculated at the coalescence points for some 3-aryl-5-alkyl-2,4-oxazolidinediones in pyridine solutions**

| | Aryl | $T$ (°C) | $\Delta G^{\neq}$ (kJ mol$^{-1}$) |
|---|---|---|---|
| 2 | o-Tolyl | 73 | 76.6 |
| 3 | 2,5-Dimethylphenyl | 74 | 77.0 |
| 4 | o-Chlorophenyl | 83 | 78.2 |
| 5 | α-Naphthyl | 90 | 79.5 |
| 8 | α-Naphthyl | 92 | 82.4 |

barriers to internal rotation about the C–N pivot bond, such that interconversion of rotamers is slow at normal temperatures. Rotational barriers in the aryloxazolidinediones are closely comparable to those reported for geometrically similar arylhydantoins.[2]

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